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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,194	02/15/2002	Michael R. Emmert-Buck	4239-61944	2881
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KLARQUIST SPARKMAN, LLP 121 S.W. SALMON STREET, SUITE #1600 ONE WORLD TRADE CENTER PORTLAND, OR 97204-2988			SANG, HONG	
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			1643	

DATE MAILED: 12/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/048,194	Applicant(s) EMMERT-BUCK, MICHAEL R.	
	Examiner Hong Sang	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 October 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-44, 46-54 and 67-69 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-44, 46-54 and 67-69 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 January 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

RE: Emmert-Buck

1. The examiner of your application in the PTO has changed. To aid in correlating of any papers for this application, all further correspondence regarding this application should be directed to Hong Sang, Art Unit: 1643.
2. Applicant's amendment filed on 10/5/2005 is acknowledged. Claims 1, 24, 44, 49, and 69 are amended. Claims 45 and 55-66 are canceled without prejudice.
3. Claims 1-44, 46-54, and 67-69 are pending and under examination.
4. The text of those sections of Title 35, U.S.Code not included in this action can be found in a prior office action.
5. Applicant's request for corrected official filing receipt in the reply filed on 10/5/2005 is acknowledged. Because applicant claims the benefit for the earlier filed provisional application, the first line of the specification should be updated accordingly.
6. Applicant's affirmation of election and amendment of the specification in the reply filed on 10/5/2005 are acknowledged.

Rejections Withdrawn

7. The rejection of claims 1-44, 49, and 67-69 under 35 U.S.C. 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because:

(a) there is a lack of correlation between the stated purpose of the method and the end result of performing the steps of the method in claim 1

(b) there is a lack of antecedent basis for the phrase “the identification of the biological molecule” in claim 1,

(c) claim 24 lacks of antecedent basis for “the components”,

(d) claim 24 lacks antecedent basis for “the cellular specimen”,

(e) claim 49 lacks antecedent basis for “the cellular substrate”,

(e) claim 69 lacks antecedent basis for “the cellular specimen”,

are withdrawn in light of applicant’s amendments to claims.

8. The rejection of claims 1-10, 12-21, 24-30, 32-42, 44, 46-54, 67, and 69 under 35 102(a) as being anticipated by Englert et al. (Cancer Res. 60:1526-1530, 2000) is withdrawn in light of applicant’s claim for the benefit of U.S. Provisional Application Number 60/145,613, filed on 7/26/1999.

9. The rejection of claims 1 and 31 under 35 103(a) as being unpatentable over Englert et al. (Cancer Res. 60:1526-1530, 2000) in view of Englert et al. (Current Opinion in Molecular Therapeutics, 1(6): 712-719, 1999, IDS) is withdrawn in light of applicant’s claim for the benefit of U.S. Provisional Application Number 60/145,613, filed on 7/26/1999.

10. The rejection of claims 1, 43 and 68 under 35 103(a) as being unpatentable over Englert et al. (Cancer Res. 60:1526-1530, 2000) in view of Huang et al. (Anal. Biochem.

268: 305-317, 1999) is withdrawn in light of applicant's claim for the benefit of U.S.

Provisional Application Number 60/145,613, filed on 7/26/1999.

11. The rejection of claims 44 and 69 under 35 102(b) as being anticipated by Imai et al. (US 5,057,438, issued 10/15/1991, IDS) is withdrawn upon further consideration.

Response to Arguments

12. The rejection of claims 1, 2, 42, and 67 under 35 102(b) as being anticipated by Imai et al. (US 5,057,438, issued 10/15/1991, IDS) is maintained.

The response states that the applicant's method requires that the "location of each of the samples that was placed on the top layer [of the membrane] was substantially preserved and reproduced on the membranes through which the samples were transferred. Their substantial retention of spatial relationship conveniently allows the resulting patterns to be correlated with the original specimens" (specification at page 23, lines 25-29, emphasis added). Thus, the method generates "a pattern that is informative about the biological molecule". As the antibodies or antigens in the biological sample disclosed in Imai are mixed randomly in an electrolyte solution and are then bound randomly to a membrane, the antibodies or antigens are not transferred to the membrane in any particular pattern that is reflective of the organization of the antibodies and antigens prior to their transfer to the membrane. Thus, Imai does not teach the generation of "a pattern that is informative about the biological molecule" and

thus does not and cannot anticipate claim 1. Claims 2, 42, and 67 depend, directly or indirectly, from claim 1 and therefore incorporate all the limitations thereof.

This argument is not found persuasive. Claims 1, 2, 42 and 67 recite "placing the biological specimen on the substrate" (see line 2, claim 1). Imai teaches that the sample solution which contains 15% sucrose was gently poured onto the reaction membrane via sample injection nozzle 12 (see column 6, lines 8-10), and the leading end of the sample injection nozzle 12 was moved to the neighborhood of the reaction membrane (see column 6, lines 11-12), therefore this limitation has been met. Although the instant specification teaches the location of each of the samples that was placed on the top layer was substantially preserved and reproduced on the membranes through which the samples were transferred, and their substantial retention of spatial relationship conveniently allows the resulting patterns to be correlated with the original specimens" (specification at page 23, lines 25-29, emphasis added), claims 1, 2, 42 and 67 do not recite this limitation that the spatial relationship of the biological specimen is preserved and reproduced through out the transfer process. Claims 1, 2, 42 and 67 only recite "transferring components of the biological specimen through the one or more deferent capture regions under conditions that allow the components to interact with the different identification molecules in the different capture regions of the substrate to produce a pattern that is informative about the biological molecule". The pattern recited in claims 1, 2, 42 and 67 can be interpreted as binding patterns such as bands or dots detected on the membrane, chromatograph, gel electrophoresis pattern, etc. Therefore, Imai teaches all the limitations of claims 1, 2, 42 and 67.

The following are NEW GROUNDS of rejection

Claim Rejections - 35 USC § 112, 2nd paragraph

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 10, 25, 44, 50, 68 and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 44, 50 and 69 recite the term "cyto coherent matrix". The meaning of "cyto coherent matrix" is unclear.

B. Claim 68 recites "the cellular specimens". There is a lack of antecedent basis for the phrase "the cellular specimens" in claim 2.

C. Claim 10 recites "multiple different discrete cellular specimens" on lines 2-3 and "a correspondence" on line 2. Does discrete mean that the specimens used are discrete or the positions of the specimens on the substrate are discrete? Moreover, the meaning of "a correspondence" is unclear. What kind of a correspondence does it indicate?

D. Claim 25 recites "reacting". Does a chemical reaction take place? Or does the reacting indicate binding or interacting?

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-4, 10, 11, 14-18, 20, 21, 24-29, 32-42, and 67 are rejected under 35 U.S.C. 102(b) as being anticipated by Christian (EP 0 139 373 A1, IDS).

Because of the indefinite nature of claims 10 and 25 (see paragraph 14 above), claims 10 is interpreted as the positions of the specimens on the substrate are discrete, and the spatial relationship between the specimens is maintained during the transfer. The “reacting” in claim 25 is interpreted as contacting an identified component with a second identification molecule.

Claims are drawn to a method of analyzing a biological specimen, comprising: placing the biological specimen on a substrate with one or more different capture regions, wherein the one or more different capture regions of the substrate contain different identification molecules that interact with different biological molecules from the biological specimen; and transferring components of the biological specimen through the one or more different capture regions under conditions that allow the components to interact with the different identification molecules in the different capture regions of the substrate to produce a pattern that is informative about the biological molecule, thereby analyzing the biological specimen.

The claims are further limited wherein the different capture regions of the substrate are layers, the biological specimen is a cellular specimen, there are at least 10 layers of the substrate, at least 100 layers of the substrate, the layers of the substrate having a thickness of at least about 25 μm , the identification molecules are antibodies that interact with the components of the cellular specimen, the cellular specimen is placed on a surface of the layered substrate prior to transferring components of the cellular specimen through the substrate, the specimen is treated prior to transferring components of the cellular specimen through the layers, to selectively transfer components through the layers, the cellular specimen comprises a cell lysate from a cell population of interest, one or more of the layers is an electrically conductive layer, the layers are separable, and are separated after transferring the components of the cellular specimen, for individualized identification of the components of the cellular specimen retained in each separated layer, the each layer is selected from the group consisting of a high concentration agarose gel, a low concentration agarose gel, a high concentration polyacrylamide gel, a low concentration polyacrylamide gel, and a membrane, the identification molecules are molecules selected from the group consisting of antibodies, nucleic acids, peptides, receptors, and ligands, the identification molecule comprises a capture molecule which retains a component of the cellular specimen in the layer, the identification molecules capture components of the transferred components in relative abundance to a quantity of the components in the cellular specimen, and provide a quantitative indication of the relative abundance of the components in the cellular specimen, the transferred components that

interact with the different identification molecules comprise intact proteins or intact nucleic acid molecules that have not been subjected to proteolytic or nucleolytic reactions prior to transfer through the different layers of the substrate.

The methods further comprising placing multiple different cellular specimens on a discrete the positions of the substrate, and the spatial relationship between the specimens is maintained during the transfer area on the substrate, wherein at least 20 different cellular specimens are placed on the surface of the substrate, correlating a pattern of interactions of different identification molecules in the different layers of the substrate with a component having known identity, identifying the components of the specimen by determining with identification molecules the components interact with, contacting an identified component with second identification molecule to determine whether the identified component is associated with an other component, wherein the cellular specimen is one or multiple tumor specimen, and the identified component is an intact protein, the components of the multiple tumor specimens are simultaneously separately transferred through the substrate, the multiple tumor specimens are specimens of a particular type of tumor at different stages of tumor progression, the multiple tumor specimens are specimens of a tumor from a particular subject at different stages of tumor progression in that subject, exposing the identification molecule to a detection molecule that associates with a combination of the capture molecule and the component of the sample, or associates with a region of the component different than a region that is recognized by the identification molecule, wherein the component is a protein, the identification molecule recognizes a first domain of the protein, and the

detection molecule recognizes the different region of the protein, wherein the detection molecule is selected from the group consisting of antibodies, nucleic acids, peptides, receptors, ligands and stains.

Christian teaches a multiple immunoassay system comprising a microassay rod adapted for screening biologic fluids for the presence of various analytes. The rod is based on a column of spaced detection layers with each detection layer including a binding amount of a known binding agent. Up to 250 or more detection layers may be formed within one rod (abstract). The system of the invention can be used to quantify substances that participate in any number of binding reactions, including antigen-antibody or nucleic acid hybridization (Page 4, lines 20-25). Numerous samples can be tested simultaneously (see page 18, lines 22 and 31). The samples can be tissue extracts (see page 21, lines 4-7). Specifically, the rod of the invention can be used to detect nucleic acid hybridization of nucleic acids attached to nitrocellulose filters (Page 7, lines 33-35). Each detection layer may include one or more reagents which can react with or otherwise provide for the detection of a desired substance (page 7, lines 14-16). Each detection layer is made up of a suitable absorbent, such as nitrocellulose, plastics, nylons, and various other synthetic fibers and supports that do not prevent binding reactions (Page 8, lines 17-28). Each detection layer may include one or more reagents, such as antibodies, which can react with or otherwise provide for the detection of a desired substance (page 5, lines 5-7, and page 7, lines 14-16). An assay rod having nine detection layers was approximately 100 microns thick (page 20, lines 13-16). A single assay rod can use some of its detection layers as internal standards,

internal positive controls and internal negative controls, which greatly aids in quantitation and in detecting false negatives and false positives (page 21, lines 18-21). After the samples bind antibodies on the substrate, a suitable enzyme-linked second antibody, such as an antibody linked to horseradish peroxidase is used to bind sample-antibodies complex which are bound to the detection layers (see page 12, lines 17-29). The reference further teaches a method for detecting the presence of substances in a test solution comprising the steps of providing an microassay rod having a plurality of spaced detection layers located at fixed spaced locations to provide a column of discrete detection layers, wherein at least one of said detection layers includes a binding amount of a known binding reagent bound thereto, said binding reagent being capable of specifically binding with one of said substances being tested for to bind said substance to said detection layer (see claim 7). The proteins extracted from different tissue samples have not been subjected to proteolytic before analyzing. Because the method of Christian can be used to analyze any tissue extracts (see page 21, lines 4-7), it is inherently capable of analyzing tumor tissue extracts.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. Claims 1-44, 46-54, 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christian (EP 0 139 373 A1, IDS) in view of Imai et al. (US 5,057,438, IDS), Okabe et al. (J. Histochem. Cytochem. 1993, 41(6):927-934), Olsen et al. (J. Immun. 1998, 220: 77-84, IDS), Manabe et al. (Anal. Biochem. 1984, 143: 39-45, IDS), Pappalardo et al. (Seminars in Radiation Oncology, 1998, 8(3): 217-223, and Huang et al. (Analytical Biochemistry, 268: 305-317, 1999).

Because of the indefinite nature of claims 44, 50, 68, and 69 (see paragraph 14 above), the "cytocoherent matrix" in claims 44, 50 and 69 is interpreted as the two dimensional orientation of the biomolecules on the membrane, and the "cellular specimens" in claim 68 is interpreted as a biological specimen.

Claims 1-4, 10, 11, 14-18, 20, 21, 24-29, 32-42, and 67 and their interpretation are set forth above (see paragraph 16).

Claims 5-9, 12-13, 19, 22-23, 30, 31, 43, 44, and 69 embody claim 1, wherein the layers are contiguous, the samples are transferred by capillary action, by electrophoresis, the components maintain a cellular architecture of the specimen as the components are transferred through the layers of the substrate, correlating interaction, the method further comprising correlating interaction between different identification molecules and the components of the cellular specimens, with a cellular architecture of the specimen, the cellular specimen is a section of a tumor, the cellular specimen is a section of a tumor, the identification molecules interact with different cellular regions of the cellular specimen, and interaction of the identification molecules is correlated with a region of the cellular specimen, the specimen is placed on a surface of the layered

substrate in a gel, and a concentration of the gel is varied to selectively transfer components of different molecular size, wherein a high concentration gel is used to selectively transfer proteins of a relatively smaller molecular size, the cellular specimen is obtained by dissecting a cell population of interest from a larger cell population, wherein dissecting a cell population of interest comprises laser capture microdissection of the cell population, the method further comprising capturing a component of the components of the cellular specimens, and performing mass spectroscopy sequencing to identify the captured component, transferring components of the biological specimen through the layered substrate produces a three dimensional matrix, wherein a surface of the substrate on which the biological specimen is placed provides the two dimensional orientation of the biomolecules on the membrane, and a third dimension is provided by transfer of components of the biological specimens through the different layers, wherein there is an identifiable correspondence between a position of the component of the biological specimen in the two dimensional orientation of the biomolecules on the membrane and a position of the transferred components in the three dimensional matrix.

Claims 46-54 are also drawn to a method of analyzing a cellular specimen, comprising: providing a substrate comprising a plurality of different layers having contiguous faces, each layer including a corresponding capture molecule capable of interacting with and capturing a component of the cellular specimen; applying the cellular specimen to a face of the substrate, and transferring intact components of the specimen through the contiguous faces of the different layers of the matrix; contacting

the intact components of the specimen with the capture molecule; and correlating a pattern of capture in the different layers with information about the cellular specimen.

The teachings of Christian are set forth above as they apply to claims 1-4, 6, 10, 11, 14-18, 20, 21, 24-29, 32-42, and 67 (see paragraph 16 above).

Christian does not teach that the sample is a tissue section, particularly tumor section, the two dimensional orientation of the biomolecules on the membranes is maintained during the transfer, transferring intact components of the specimen comprises transferring by capillary action and the substrate layers are contiguous, by electrophoresis, the concentration of the gel is varied to selectively transfer components of different molecular size, the cellular specimen is obtained by dissecting a cell population of interest from a larger cell population by laser capture microdissection of the cell population, and use mass spectroscopy sequencing to identify the captured component. However these deficiencies are made up for in the teachings of Imai, Okabe, Olsen, Manabe, Pappalardo, and Huang.

Imai teaches a method for determination of a plurality of species of antibodies or antigens with laminate of multiple electrophoretic carriers each having a different species of antibody or antigen (see abstract). An electrophoretic carriers can be polyacrylamide gel, agarose gel, etc. (see column 3, lines 63-64). The substrate layers are contiguous. The transfer is effected by means of electrophoresis or may be attained without any recourse to electrophoresis (see column 4, lines 50-57).

Okabe et al. teach a method for direct transfer of native proteins from unfixed frozen tissue sections to an immobilizing matrix, e.g. nitrocellulose, polyvinyliden

difluoride or positively charged nylon membranes. Proteins are directly blotted onto the membrane, providing optimal accessibility from molecular detection by retaining the anatomic localization at the cellular level (see abstract). Okabe et al. further teaches that selective binding of proteins can be induced by pre-coating the blotting membranes with ligands, such as lectins, hormones, synthesized peptides, or drugs, and this way a more selective binding of macromolecules from the tissue to membrane may be achieved (see page 934, last paragraph, last two sentences).

Olsen et al. teach a method for diffusion blotting of proteins from precast SDS-Page gels to nitrocellulose membranes. From one gel with 20 lanes one can obtain at least 200 imprints. Under optimal conditions it should be possible to increase the number of imprints made from a single lane (see page 83, left column, lines 8-10). The number of imprints which can be obtained is dependent on the sensitivity of the detection system and the amount of protein applied. The great advantage of diffusion blotting compared to electroblotting is that several imprints can be made from each lane and different antisera can be tested on identical imprints (see abstract, and page 78, last paragraph).

Manabe et al. teach a method for electrophoretic transfer of proteins from micro polyacrylamide slab gels to nitrocellulose sheets. By using this method multiple replica from a gradient gel is obtained (see abstract). The serum proteins are applied on the gradient gel (4-17% acrylamide gradient and 0.2-0.85% N,N'-methylenebisacrylamide gradient) (see page 41, right column, last paragraph, and Fig.2). Manabe et al. further

teach that in order to obtain multiple replica from a gel, uniform transfer of proteins to nitrocellulose sheets is most desirable (see page 43, last paragraph).

Pappalardo et al. teach laser capture microdissection (see page 217, right column, and Figures 1 and 2) and its application in microchip arrays and molecular analysis of tumor cells (see abstract).

Huang et al. teach that mass spectrometry sequencing is of potential use for obtaining sequence information directly from mixtures or as an adjunct of peptide mass mapping to provide protein identification with high confidence (see abstract).

It would have been *prima fascia* obvious to one skilled in the art at the time the invention was made to have modified the methods of Imai or Christian by analyzing tissue sections, using laser capture microdissection or mass spectroscopy sequencing in view of the teachings of Okabe, Pappalardo and Huang because using tissue sections can not only identify the molecules but also provide the information of anatomic localization at the cellular level cell as taught by Okabe et al, laser capture microdissection is known in the art for the purpose of obtaining isolated defined cell types from a sample as taught by Pappalardo et al, mass spectrometry sequencing of proteins is known in the art as a powerful tool for protein identification as taught by Huang. One would have been motivated to modify the methods of Imai or Christian by using tissue sections, or laser capture microdissection for the purpose of obtaining further cellular architectural information, or purifying samples to a specific cell type before transfer because histological tissues can be complex, leading to complexity of the molecular analysis. One would have been motivated to use the method of Huang

for the further identification of captured proteins because Huang teaches that mass spectroscopy sequencing is useful for analysis of a sample that is a heterogeneous mixture. Additionally one would have had a reasonable expectation of success at the time the invention was made to have modified the methods of Imai or Christian by analyzing tissue sections, using laser capture microdissection or mass spectroscopy sequencing in view of the teachings of Okabe, Pappalardo and Huang because those methods have been used successfully by each of them.

It would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have modified the methods of Imai or Christian by varying the concentration of the gel to selectively transfer components of different molecular size in view of the teachings of Manabe et al. One would have been motivated to modify the methods of Imai or Christian by varying the concentration of the gel because Manabe teaches that in order to obtain multiple replica from a gel, uniform transfer of proteins to nitrocellulose sheets is most desirable (see page 43, last paragraph). Moreover one would have had a reasonable expectation of success at the time the invention was made to modify the methods of Imai or Christian by varying the concentration of the gel to selectively transfer components of different molecular size because Manabe et al. teach how to make and use gradient gel and transfer samples from the gradient gel to multiple membranes.

Moreover, one would have had a motivation to modify the method of Christian by using substrate having contiguous layers and capillary transfer or by electro-transfer because contiguous layers facilitate the capillary transfer, reduce the nonspecific

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binding that could occur in the space layer, which reduces the amount of sample required for analysis, capillary transfer is good for nucleic acid analysis, electro-transfer is well known method for protein transfer that is quick and efficient. One would have had a reasonable expectation of success at the time the invention was made to transfer the samples by using contiguous layered substrates and capillary transfer or electro-transfer because both Imai and Olson teach a method of transferring samples using multiple contiguous layers by capillary and electrophoresis.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

20. Claims 1-6, 8-21, 24, 32-37, 40-42, 44, 46-54, 67 and 69 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 12-14, 16, 19, 21, 23-27, and 30-32 of U.S. Patent No. 6,602,661 in view of Christian (EP 0 139 373 A1, IDS).

Claims 1-6, 8-21, 24, 32-37, 40-42, 44, 46-54, 67 and 69 and their interpretation are set forth above (see paragraphs 16 and 18)

Claims 1-7, 12-14, 16, 19, 21, 23-27, and 30-32 of U.S. Patent No. 6,602,661 are drawn to a method of making multiple substantial replicas of a biomolecular content of a sample, comprises (a) providing a stack of membranes (50 or more), (b) providing a tissue section containing biomolecules, which biomolecules have a relative relationship to each other in at least two dimensions within the tissue section, (C) applying the tissue section to the plurality of membranes under conditions that allow multiple membranes to capture at least a portion of the biomolecules from the tissue section so as to create multiple substantial replicas of the biomolecular content of the tissue section and therein each of the substantial replicas maintains the relative relationship of the biomolecules. The claims are further limited wherein one or more of said membranes comprise a material for increasing an affinity of at least one of said membranes to the biomolecules, the thickness of the membrane is less than 30 microns and no less than 4 microns. The method further comprising detecting at least one biomolecules of interest on at least one of said multiple membranes, wherein the detecting said biomolecules comprises separating one or more of said membranes from said stack, and detecting said

biomolecules on one or more of the separated membranes. Claims are also drawn to a method of making multiple substantial replicas of a biomolecular content of a sample, wherein said sample is a microarray, and the microarray comprises a plurality of DNA probes, antibodies or a combination thereof.

Claims 1-7, 12-14, 16, 19, 21, 23-27, and 30-32 of U.S. Patent No. 6,602,661 fail to teach that one or more different capture regions of the substrate contain identification molecules. However these deficiencies are made up for in the teachings of Christian (EP 0 139 373 A1).

Christian teaches a multiple immunoassay system comprising a microassay rod adapted for screening biologic fluids for the presence of various analytes. The rod is based on a column of spaced detection layers with each detection layer including a binding amount of a known binding agent. Up to 250 or more detection layers may be formed within one rod (abstract). The system of the invention can be used to quantify substances that participate in any number of binding reactions, including antigen-antibody or nucleic acid hybridization (Page 4, lines 20-25). Numerous samples can be tested simultaneously (see page 18, lines 22 and 31). The immunoassay carried out in each detection layer may be directly measured by a suitable detection system (Page 7, lines 15-20). Each detection layer is made up of a suitable absorbent, such as nitrocellulose, plastics, nylons, and various other synthetic fibers and supports that do not prevent binding reactions (Page 8, lines 17-28). Each detection layer may include one or more reagents which can react with or otherwise provide for the detection of a desired substance (page 7, lines 14-16).

It would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have modified the methods of claims 1-7, 12-14, 16, 19, 21, 23-27, and 30-32 of U.S. Patent No. 6,602,661 by using substrate containing different identification molecules in view of the teachings of Christian. One would have been motivated to modify the methods of claims 1-7, 12-14, 16, 19, 21, 23-27, and 30-32 of U.S. Patent No. 6,602,661 by using the substrate containing different identification molecules because Christian teaches that by using substrates containing different identification molecules, different biomolecules in the test samples can be selectively bound to different identification molecules on the membranes, screened and identified conveniently, quickly, effectively and accurately (see page 4, 1st and 2nd paragraph). Additionally one would have a reasonable expectation of success to modify the methods of claims 1-7, 12-14, 16, 19, 21, 23-27, and 30-32 of U.S. Patent No. 6,602,661 because Christian teaches how to make the substrate containing the different identification molecules, and the method of detecting biomolecules in a samples by transferring the samples to said multiple substrates and further detecting them.

Claims 1-6, 8-21, 24, 32-37, 40-42, 44, 46-54, 67 and 69 directed to an invention not patentably distinct from claims 1-7, 12-14, 16, 19, 21, 23-27, and 30-32 of commonly assigned US Patent No. 6,602,661B1 for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/648,694, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the

commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should


you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

Hong Sang

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Nov. 28, 2005



LARRY R. HELMS, PH.D.
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